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ulating two receptors with key roles in worm motility, these EOs emerge as novel sources of anthelmintic compounds. To unequivocally confirm that these receptors are targets of TC and to describe the mechanism by which they affect these receptors, we performed whole-cell and single-channel recordings from *C. elegans* muscle cells. Electrophysiological recordings at the single-channel level revealed that TC reduces L-AChR channel activity without affecting channel properties. The results are compatible with the action of these drugs as allosteric inhibitors. It is hoped that this work can update the recent progress on natural nematicide discoveries and provide new ideas for the design and mechanism of action studies of anthelmintics.

91. (284) **DEVELOPMENT AND ASSESSMENT OF THE COENCAPSULATION OF CARVEDILOL AND CURCUMIN IN A NANOMICELLAR DISPERSION SYSTEM IN AN EXPERIMENTAL MODEL OF HYPERTENSION.**

Yanina Santander Plantamura[1,2], Miguel Ángel Allo[1,2], Jennifer Riedel[2,3], Pedro Fuentes[2,3], Marcela Moretton[2,3], Diego Chiappetta[2,3], Christian Höcht[1,2], Susana Gorzalczany[1,2]

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Carvedilol is a third-generation ß-blocker with pleiotropic effects, including antioxidant, anti-inflammatory and anti-apoptotic effects. Curcumin is a phenolic compound belonging to turmeric, with a beneficial effect on blood pressure. The objective of the present work was the development and assessment of the pharmacokinetic (PK) and pharmacodynamic (PD) profile of the coencapsulation of carvedilol and curcumin in nanomicellar dispersions of Soluplus in spontaneously hypertensive rats (SHR).

Nanomicellar dispersions of 10% w/v Soluplus containing carvedilol 3 mg/ml, curcumin 2 mg/ml , or both were prepared using the solvent evaporation technique. Plasma pharmacokinetics and hemodynamic response after oral administration of carvedilol 9 mg/kg, curcumin 6 mg/kg or carvedilol/curcumin 9/6 mg/kg were assessed in 20 male SHR rats after carotid artery cannulation.

Results: Plasma curcumin levels were comparable after coadministration of carvedilol/curcumin or curcumin only. Coencapsulation did not modify the PK profile of carvedilol. Curcumin oral administration did not induce changes in blood pressure and heart rate. Coencapsulation resulted in a greater MAP reduction when compared with carvedilol (-28,5±4,0 % vs –12,1±3,1%, $p<0.05$). HR reduction was comparable after oral administration of carvedilol or coencapsulation.

Conclusions: Coencapsulation of curcumin with carvedilol in nanomicellar dispersions potentiates the antihypertensive effect of carvedilol without modifying the bradycardic responser nor the pharmacokinetic profile. These results suggest that coencapsulation of carvedilol and curcumin represents a potential pharmacodynamic synergistic combination for the management of arterial hypertension.

92. (305) **MOD-1 RECEPTOR AS A NOVEL DRUG TARGET FOR ANTHELMINTIC THERAPY**

Noelia Rodriguez Araujo, Guillermina Hernando, Jeremías Corradi and Cecilia Bouzat.

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Caenorhabditis elegans (Nematoda) contains a homomeric 5HT-gated chloride channel, MOD-1, that belongs to the Cys-loop receptor family and modulates locomotor behavior. Although it binds 5-HT, MOD-1 is not present in vertebrates, and it therefore emerges as a possible anthelmintic target. We deciphered MOD-1 pharmacological properties and searched for novel modulators with potential anthelmintic activity by performing patch-clamp recordings from mammalian cells heterologously expressing MOD-1 and locomotor activity assays in *C. elegans*. Whole-cell recordings showed that MOD-1 desensitizes slowly and recovers from desensitization with a time constant of about 1 s. Compared to the vertebrate 5-HT_3A receptor, dose-response curves were similar for 5-HT but very different for the orthosteric agonists tryptamine and 2-Me-5HT. The anthelmintic drugs ivermectin (IVM), levamisole, and piperazine (PZE), which are agonists of other Cys-loop receptors, did not activate MOD-1. However, IVM produced a slight and irreversible inhibition and PZE produced a profound and reversible inhibition of MOD-1 currents elicited by 5-HT. The analysis indicated that PZE is a non-competitive antagonist of MOD-1, revealing a novel function of this drug. To relate the molecular effects to behavioral actions of these compounds, we performed locomotor activity assays in *C. elegans*. We found that 5-HT produces rapid and reversible paralysis of wild-type (WT) worms while MOD-1 mutants are partially resistant under similar conditions, thus indicating that MOD-1 is the main 5-HT target in this type of assays. Additional assays using drug combinations in WT and mutant strains confirmed the inhibition of MOD-1 activity by IVM and PZE. The elucidation of the molecular pharmacology of MOD-1 enhances our knowledge of function and drug selectivity of Cys-loop receptors and contributes to determine its potential as a novel target for anthelmintic therapy.

93. (390) **RATIONAL SEARCH FOR G PROTEIN-COUPLED RECEPTOR KINASE 5 INHIBITORS UTILIZING DOKING-BASED VIRTUAL SCREENING**

Emiliana Echeverría[1], Sonia Ripoll[1], Maia Cabrera[2], Pablo Lorenzano-Menna[2], Natalia Fernández[1].

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G protein-coupled receptor (GPCR) kinase 5 proved to be overexpressed in failing hearts causing increased desensitization of beta-adrenergic receptors (βARs), deficit in cardiac contractility and failure progression. It has two main domains: Regulator of G protein Signaling (RGS) homology domain (RH), and protein kinase domain (KD). The mechanism of GPCRs phosphorylation by GRK5 requires the disruption of an ionic lock in RH/KD interface, leading to a more stable complex with the GPCR that enhances catalytic properties of the kinase.

To obtain GRK5 inhibitors we performed a docking-based virtual screening (VS) using pdb ID 4TND to search within Enamine Advanced Collection for compounds able to bind to RH/KD interface, intending to strengthen ionic lock and avoid the catalytically competent conformation to be reached. We obtained a list of hits ordered by docking energy, ranging from -10.4 to -9.7. Using Protein Ligand Interaction Profiler tool, we evaluated non-covalent interactions between GRK5 and predicted docking poses, and observed several hydrophobic interactions and hydrogen bonds joining residues from RH and KD. Also, interesting interactions such as salt bridges, halogen bonds and π-cation were found. Accordingly, we chose 15 compounds to be purchased and evaluated in biological activity assays, for what we setted up FRET-based determinations to quantify real-time intracellular cAMP. HEKT Epac-SH187 cells co-transfected with GRK5 and β1AR or β2AR were stimulated with 10μM isoproterenol (Iso) and AUC (area under curve) values of 10min response were determined in FlexStation3 at 37°C. AUCs were reduced from 244.4±24 to 112.5±7.4 for β1AR and from 138.7±10 to 64.73±3.45 for β2AR ($p<0.05$) by GRK5 overexpression (confirmed by Western Blot).

Both computer aided identification of potential GRK5 ligands and obtention of a methodology for screening these compounds will allow us to identify candidate inhibitors of GRK5 in the search of new cardioprotective drugs.

94. (476) **BIOACTIVITY OF ALPHA-HALOACRYLATES OF METYL BETA-SUBSTITUTED SYNTHETIZED *DE NOVO* IN AN *IN VITRO* MODEL OF MAST CELL DEGRANULATION**